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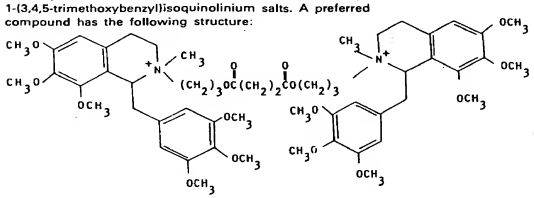
(54) **Long duration neuromuscular blocking agents, pharmaceutical compositions containing them and processes for their preparation.**

(57) This invention relates to long duration neuromuscular blocking agents, known examples of which agents have been found to have cardiovascular and other side effects, and seeks to overcome the shortcomings of presently used agents. The compounds of this invention are *trans, trans*-2,2'-(dimethylene*bis*(carbonyloxy-trimethylene))*bis*(1,2,3,4-tetrahydro-6,7,8-trimethoxy-2-alkyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium salts. A preferred compound has the following structure:



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LONG DURATION NEUROMUSCULAR BLOCKING AGENTS, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESSES FOR THEIR PREPARATION

In anesthesia, neuromuscular blocking agents are used to provide skeletal muscle relaxation during surgery and during intubation of the trachea.

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In general there are two types of neuromuscular blocking agents in use, non-depolarizing and depolarizing.

The non-depolarizing agents include d-tubocurarine, pancuronium, gallamine, diallyltoxiferine and toxiferine.

The depolarizing agents include succinylcholine and decamethonium. All of the conventional non-depolarizing agents when used for producing skeletal muscle relaxation in surgery have a long duration of action, e.g. 60 to 180 minutes in man. The conventional depolarizing agents, on the other hand, provide muscle relaxation with duration of action shorter than that of the non-depolarizing agents.

For example, succinylcholine provides a short duration of action of about 5 to 15 minutes whereas decamethonium provides about 20 to 40 minutes duration of muscle relaxation in man.

Each non-depolarizing agent has inherent side effects. For example, gallamine and pancuronium may cause tachycardia, and d-tubocurarine and diallyltoxiferine may cause hypotension.

While these drugs can be pharmacologically antagnoized with anti-cholinesterase agents, this obviously necessitates the administration of a second drug which itself may have its own side effects, e.g. bradycardia, gut spasm and bronchorrhea. Thus, to overcome the aforementioned side effets of the anticholinesterase agents, a third drug, an anticholinergic drug, e.g. atropine must also be given.

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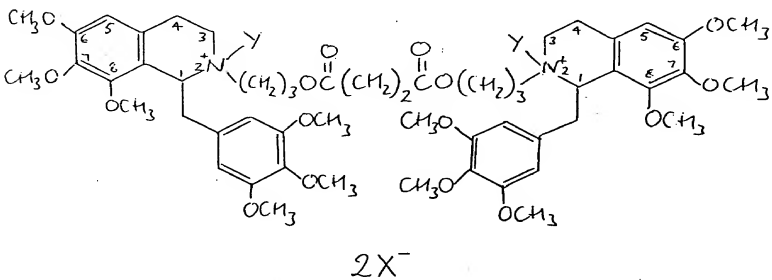
Suprisingly, the compounds of the present invention have a very high potency, long duration of action and are apparently free of any side effects at the dosages anticipated being used clinically. Furthermore, the trans compound where Y is methyl has shown unexpectedly superior activity (potency) and suprisingly much longer duration than any of their analogues, i.e., compounds with different chain lengths and the same isoquinoline base or compounds with different bases and the same chain length.

According to a first aspect of the present invention, there are provided new neuromuscular blocking agents (sometimes called muscle relaxtants) of the formula (I):



$2X^-$

(I)

wherein Y represents a lower alkyl group of 1 to 4 carbon atoms (methyl, ethyl, propyl or butyl); X^- is an anion, preferably pharmaceutically acceptable; and preferably the trimethoxybenzyl group at the 1 position and the proximal $(CH_2)_3$ (also known as substituted propyl) moiety of the group $(CH_2)_3OCO(CH_2)_2OCO(CH_2)_3$

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at the 2 position are in a trans relationship with each other in each nitrogen-containing ring.

The preferred compound is that wherein Y represents a methyl group.

Since the activity of the compounds of the invention resides in the di-cation, the nature of the anion X^- is relatively unimportant. Suitable pharmaceutically acceptable anions include iodide, mesylate, tosylate, bromide, chloride, sulphate, phosphate, hydrogen phosphate, acetate, benzenesulphonate, succinate, maleate, naphthalenesulphonate and propionate.

The compounds of the invention are preferably prepared as an approximately 1:1 mixture of the racemic (dl) pair and the meso-isomer. This invention further provides means for obtaining the compounds of formula (I) when in the form of one of the aforesaid isomers substantially free of the other isomers, and mixtures of one of the isomers with one or both of the other isomers. Other methods of preparing the cis-trans mixtures are well known in the art.

It is preferred that the compounds of the invention be provided in a form where the ratio of the trans, trans compound of the invention to the total of any corresponding cis, cis and cis, trans compounds present as impurtities is at least 96:4.

The compounds of formula (I) may be used as neuromuscular blocking agents in conjunction with surgery or for intubation of the trachea by conventional parenteral administration, e.g. intramuscular or intravenous administration in solution. According to a second aspect of the present invention, therefore, there is provided a compound in accordance with the first aspect for use as a neuromuscular blocking agent. The compounds of the present invention shown in formula (I) are administered to subjects such as monkeys and man (humans)

and other mammals to achieve a neuromuscular block. The dosage for each type of subject will vary because of the peculiarities of the species. However, a suitable intravenous amount or dosage of the compounds of formula (I) to obtain paralysis in mammals would be 0.004 to 0.03 mg/kg of body weight, and most preferably 0.01 to 0.02 mg/kg of body weight, the above being based on the weight of the di-cation which is the active ingredient. The compounds of this invention appear, therefore, to be clearly more potent than the agents most widely used clinically (pancuronium 0.06-0.08 mg/kg, d-tubocurarine 0.4-0.6 mg/kg). The dosage for intramuscular administration is two to four times the intravenous dose. The compounds of this invention are reversible using conventional anti-cholinesterase agents such as neostigmine and edrophonium and appear to avoid the side effects associated with the non-depolarizing agents.

The compounds of formula (I) are therefore useful for producing a long duration neuromuscular blockade in man as well as in other mammals, and the present invention provides a method of producing such blockade in mammals by intravenously injecting a dose of 0.004 to 0.03 mg/kg to the mammal. It should be understood that the duration in a mammal such as monkey is considerably shorter than in humans and is considered a long duration agent for that species.

The compounds may be presented in a pharmaceutical formulation for parenteral administration. The formulations may be an aqueous or non-aqueous solution or emulsion in a pharmacetically acceptable liquid or mixture of liquids, which may contain bacteriostatic agents, antioxidants, buffers, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such formulations are normally presented in unit dosage forms such as ampoules or disposable injection devices, or in multidose forms such as a bottle from which the appropriate dose may be withdrawn; all such formulations should be sterile.

The compounds of this invention may be presented as a powder, e.g. as a unit dose in a sealed vial to which sterile water or an other pharmacetically acceptable sterile liquid vehicle may be added, preferably by aseptic techniques.

A suitable unit dose to obtain a neuromuscular block for adult humans (~150 lb) is about 0.15 mg to 2.5 mg and most preferably 0.5 to 1.5 mg.

The compounds of this invention if desired may be administered in conjunction with depolarizing agents such as listed above.

Thus a suitable pharmaceutical parenteral preparation for administration to humans will preferably contain 0.3 to 2.5 mg of the compounds of formula (I) of this invention in solution.

A simple and preferred formulation is a solution of the compound of formula (I) in water which may be prepared by simply dissolving the compound into previously sterilized pure water (i.e. pyrogen free water), under aseptic conditions, and sterilizing the solution.

The compound of formula (I) may also be administered as an infusion of a dextrose solution or a saline solution, e.g. Ringers' solution.

The compounds may also be administered in other solvents such as alcohol, polyethylene glycol and dimethylsulphoxide. They may also be administered intramuscularly as a suspension.

According to another aspect of the present invention, there is provided a process for the preparation of the compounds of formula (I), as defined above, which process comprises either

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A. effecting the coupling of two trans-N-(C_1 to C_4)alkyl-N-3-hydroxypropyl-1,2,3,4- tetrahydro-6,7,8-trimethoxy-1-(3,4,5-trimethoxybenzyl)-isoquinolinium ions with succinic acid or a reactive derivative thereof; or

B. effecting the coupling of two trans-N-(C_1 to C_4)alkyl-N-3-halopropyl-1,2,3,4-tetrahydro-6,7,8-trimethoxy-1-(3,4,5-trimethoxybenzyl)-isoquinolinium ions with the di-silver salt of succinic acid.

Suitable reactive derivatives of succinic acid are succinic anhydride and succinyl chloride.

The coupling of the 3-halopropyl compounds using the disilver salt of succinic acid may be carried out in a manner similar to that desribed in US Patent No. 4,192,877.

For a better understanding of the present invention, the following Examples are given.

Example 1

5',8-Dimethoxylaudanosine (27.2 g) and iodopropanol (27.2 g) were refluxed in 150 ml of dry acetone for 21 hours. The solvent was evaporated under vacuum and the unreacted iodopropanol was extracted with 100 ml of diethyl ether. The ether was decanted and the residue was dissolved in 300 ml of hot ethyl alcohol and cooled at 5^{o} for 16 hours to yield 29.2 g of a 9/1 mixture of the trans-cis quaternary iodides as indicated by High Performance Liquid Chromatography (HPLC). The mixture was recrystallized twice from ethyl alcohol to give 24.4 g of trans-N-3-hydroxypropyl-5',8-dimethoxylaudanosinium iodide (98% trans by HPLC). The iodide salt was converted to the chloride salt by passing its methanolic solution through a column packed with

75 g of Dowex 1-X8 ion exchange resin. The solvent was evaporated under vacuum and 100 ml of acetone was added to give 18.1 g of trans-N-3-hydroxypropyl-5',8-dimethoxylaudanosinium chloride (100% trans by HPLC). The yield was 67% overall.

Calculated for $C_{26}H_{38}NO_7Cl_2 2H_2O$: C, 56.98; H, 7.72; N, 2.56; Cl, 6.47. Found: C, 56.97; H, 7.74; N, 2.52; Cl, 6.47.

Example 2

Trans-N-3-hydroxypropyl-5',8-dimethoxylaudanosinium chloride (99% trans by HPLC, 2 g) was suspended in 150 ml of 1,2-dichloroethane at ~70° and succinyl chloride (0.24 g) was added. The mixture was heated at reflux for 140 minutes. The solvent was removed under vacuum to give an amorphous solid which was dissolved in 100 ml of chloroform and washed with 5% aqueous sodium chloride solution 8 x 100 ml to remove the unreacted quaternary salt. The chloroform layer was washed with 50 ml of water, dried and evaporated under vacuum. The residual amorphous solid was dissolved in water and lyophilized to give 0.51 g of trans, trans-2,2'-(dimethylenebis(carbonyloxytrimethylene))bis (1,2,3,4,-tetrahydro-6,7,8-trimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium) dichloride which was assyed by High Performance Liquid Chromatography (HPLC) as 100%.

Calculated for $C_{56}H_{78}N_2O_{16}2\,Cl\,6\,H_2O$: C, 55.39; H, 7.47; N, 2.31; Cl, 5.83. Found: C, 55.72; H, 7.04; N, 2.27; Cl 5.84.

Example 3

Mescaline and 3,4,5-trimethoxyphenylacetic acid were reacted in xylene to give the corresponding amide which was cyclized to the corresponding dihydroisoquinoline via the Bischler-Napieralski reaction followed by reduction and reductive methylation to give 5',8-dimethoxylaudanosine mp 174-176.

Example 4

trans, trans-2,2'-(Dimethylenebis(carbonyloxytrimethylene))-bis(1,2,3,4-tetrahydro-6,7,8-trimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium) dichloride was examined by intravenous administration to cats and Rhesus monkies, maintained by artificial ventilation and prepared for recording the isometric twitch of the tibialis anterior muscle in responce to stimulation of the peroneal nerve. The results are shown in the following tables.

	Cat			Rhesus Monkey		
No. of Animals	ED_{95} mg/kg	Duration Minute	No. of Animals	ED_{95} mg/kg	*Duration Minute
2	0.01	~60	2	0.015	~30+

*The time from injection to 95% recovery

+This translates to about 90 minutes in man.

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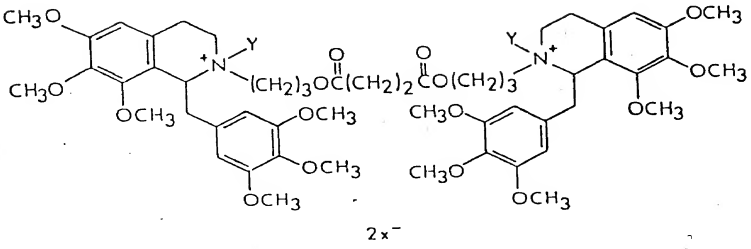
CLAIMS

1. A compound characterized by formula (I):



(I)

wherein Y represents lower alkyl group of 1 to 4 carbon atoms and X represents an anion.

2. A compound according to Claim 1, characterized in that, for each of the nitrogen containing rings, the trimethoxybenzyl group at the 1 position and the group $(CH_2)_3OCO(CH_2)_2OCO(CH_2)_3$ at the 2 position are in a trans relationship with each other.

3. A compound according to Claim 1 or 2, characterized in that Y represents a methyl group.

4. A compound according to Claim 1 or 2, characterized in that X represents a pharmaceutically acceptable anion.

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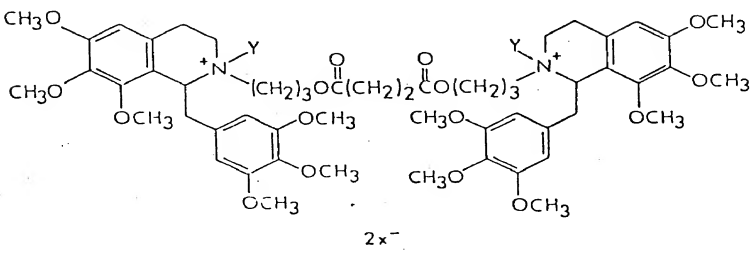
5. A mixture comprising the mixture of the racemic (dl) pair and the meso-isomer of the compound characterized by formula (I):



(I)

wherein Y represents a lower alkyl group of 1 to 4 carbon atoms and X represents an anion.

6. A mixture according to Claim 5, characterized in that Y represents a methyl group and X represents a pharmaceutically acceptable anion.

7. A compound characterized by formula (I)

(I)

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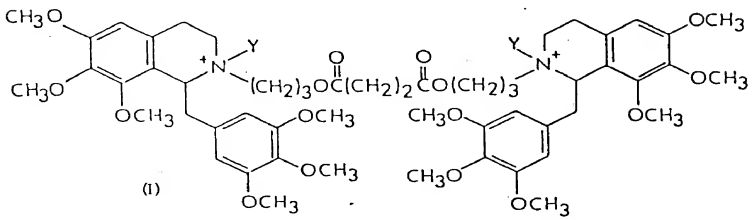
wherein Y represents a lower alkyl group of 1 to 4 carbon atoms and X represents an anion, for use as a neuromuscular blocking agent.

8. A pharmaceutical composition comprising one or more active ingredient and a pharmaceutically acceptable carrier, characterized in that the or each or an active ingredient is a compound of formula (I).

9. A process for preparing a compound of formula (I):



(I)

characterized by either

A. effecting the coupling of two trans-N-(C_1 to C_4)alkyl-N-3-hydroxypropyl-1,2,3,4-tetrahydro-6,7,8-trimethoxy-1-(3,4,5-trimethoxybenzyl)-isoquinolinium ions with succinic acid or a reactive derivative thereof; or

B. effecting the coupling of two trans-N-(C_1 to C_4)alkyl-N-3-halopropyl-1,2,3,4-tetrahydro-6,7,8-trimethoxy-1-(3,4,5-trimethoxybenzyl)-isoquinolinium ions with the di-silver salt of succinic acid.

10. A process according to Claim 9 A, characterized in that the coupling is effected with succinic anhydride or succinyl chloride.

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EUROPEAN SEARCH REPORT

0054309
Application number
EP 81110513.9

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.³)
	GB - A - 863 717 (ALLEN & HANBURYS) * Page 1, lines 9-44 * --	1,7,9	C 07 D 217/20 A 61 K 31/47
	GB - A - 1 579 822 (THE WELLCOME) (26-11-1980) * Page 2, line 7 - page 3, line 5; page 5, lines 16, 17 * --	1,7,8	
D	US - A - 4 192 877 (SAVARESE) * Abstract; column 4, line 67 - column 5, line 60 * ----	1,3,4, 7-9	TECHNICAL FIELDS SEARCHED (Int. Cl.³) C 07 D 217/00

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	15-02-1982	ONDER

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